



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 16, 312, 511, and 812

[Docket No. FDA-2011-N-0079]

RIN 0910-AG49

Disqualification of a Clinical Investigator

AGENCY: Food and Drug Administration, HHS

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the regulations to expand the scope of clinical investigator disqualification. Under this rulemaking, when the Commissioner of Food and Drugs (the Commissioner) determines that an investigator is ineligible to receive one kind of test article (drugs, devices or new animal drugs), the investigator also will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for other kinds of products regulated by FDA. This final rule is based in part upon recommendations from the Government Accountability Office (GAO), and is intended to help ensure adequate protection of research subjects and the quality and integrity of data submitted to FDA. FDA also is amending the list of regulatory provisions under which an informal regulatory hearing is available by changing the scope of certain provisions and adding regulatory provisions that were inadvertently omitted.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT:

Kathleen E. Pfaender,
Office of Good Clinical Practice,
Food and Drug Administration,
10903 New Hampshire Ave.,
Bldg. 32, rm. 5129,
Silver Spring, MD 20993,
301-796-8340.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of April 13, 2011 (76 FR 20575), FDA proposed to amend its regulations to expand the scope of clinical investigator disqualification (the April 2011 proposed rule). As discussed in greater detail in the preamble to the proposed rule (76 FR 20575 at 20576 to 20585), when disqualified by a Commissioner's decision under one part of the former regulations a clinical investigator continued to be eligible to receive other types of test articles and conduct clinical investigations studying those other test articles.

The GAO, in its September 2009 final report on FDA's oversight of clinical investigators (Ref. 1), recognized FDA's regulatory limitations regarding clinical investigator disqualification. In its September 2009 final report, the GAO recommended, among other things, that FDA extend disqualification by a Commissioner's decision to include ineligibility to receive unapproved drugs, biologics, and medical devices. The GAO concluded that it is "critical for FDA to take action--and to have the authority to take action--to prevent clinical investigators * * * who engaged in serious misconduct from doing so again, whether in research that involves drugs, biologics, or devices" (Ref. 1, at page 42). Among other amended provisions, this final rule

responds to that GAO report and prevents clinical investigators who are disqualified by a Commissioner's decision (whether related to drugs, biologics, devices, or animal drugs) from conducting any clinical investigations that support an application for a research or marketing permit for products regulated by FDA. The other amended provisions in this final rule provide for clarity and harmonization of the clinical investigator disqualification regulations and the addition of inadvertently omitted regulatory provisions under which a part 16 (21 CFR part 16) regulatory hearing is available.

II. Overview of the Final Rule

This final rule amends part 312 (21 CFR part 312) in § 312.70, part 511 (21 CFR part 511) in § 511.1(c), and part 812 (21 CFR part 812) in § 812.119) to provide that when the Commissioner determines that a clinical investigator is ineligible to receive the test article under that part (e.g., new animal drugs in part 511 or drugs in part 312), the clinical investigator also is ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

Other amendments in this final rule, as explained in the preamble to the proposed rule, help to clarify and harmonize the clinical investigator disqualification regulations in parts 312, 511, and 812 (21 CFR part 812). Also, this final rule amends certain provisions in part 16 (21 CFR part 16) by:

- Adding to § 16.1(b)(2) an entry for § 812.119;
- Revising the entries for §§ 312.70 and 511.1(c)(1); and

- Adding to the list of regulatory provisions under which a part 16 regulatory hearing is available, provisions for:
 - § 58.204(b) (21 CFR 58.204(b)), relating to disqualifying a testing facility, and
 - § 822.7(a)(3) (21 CFR 822.7(a)(3)), relating to an order to conduct postmarket surveillance of a medical device under section 522 of the Federal Food Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 360l).

On its own initiative, FDA modified the codified language published in the April 2011 proposed rule (76 FR 20575), to remove “pursuit of” from the proposed provisions in §§ 312.70(a), 511.1(c)(1), and 812.119(a). FDA made this change to clarify the rule and eliminate unnecessary language. In this final rule, therefore, the relevant language is “If an explanation is offered and accepted by the applicable Center, the Center will discontinue the disqualification proceeding” (see in this document codified §§ 312.70(a), 511.1(c)(1), and 812.119(a)).

This final rule helps to protect the rights and safety of subjects involved in FDA-regulated investigations, and helps to ensure the reliability and integrity of the data used to support marketing of products regulated by FDA.

III. Comments on the Proposed Rule

FDA received two comments on the proposed rule: One from a healthcare professional and the other from regulated industry. Both submissions supported the proposal to help ensure adequate protection of research subjects and the quality and integrity of data submitted to FDA. The healthcare professional supported the proposal and had no other comment. The following comments and responses summarize and address the issues found in the submission from regulated industry:

(Comment 1) The comment suggests that FDA either clarify or define the terms “repeatedly or deliberately” or alternatively consider removing the language from § 812.119(a). The comment further asks that FDA consider how much data or what frequency constitutes “repeatedly”; and for “deliberately”, how FDA proposes to determine deliberate actions. The comment requests examples.

(Response) The interpretations of the terms “repeatedly” and “deliberately” in FDA’s regulations governing disqualification of clinical investigators are well established. The term “repeatedly” means, simply, more than once.¹ A violation occurs “repeatedly” if it happens more than once.²

FDA may consider disqualification if a clinical investigator commits a regulatory violation more than one time within a single study (e.g., enrolling in a single study two study subjects who were ineligible because of concomitant illnesses that put those subjects at greater risk) or one time in each of two studies (e.g., enrolling in each of two studies, a study subject who was ineligible because of a concomitant illness putting the subject at greater risk). The Commissioner, in past decisions, has determined that multiple violations within a single study constitute repeated violations sufficient to support disqualification from receipt of test articles.³

¹ See, e.g., Commissioner’s Decision, In the Matter of William H Ziering, M.D. (2008), at page 7. “The term ‘repeatedly,’ as it is used in 21 CFR 312.70(b), is given its plain meaning, such that a clinical investigator may be found to have acted ‘repeatedly’ if he or she engages in proscribed conduct ‘more than once.’” (<http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM144019.pdf>).

² See, In The Matter of James A. Halikas, Jr., M.D., Commissioner’s Decision (January 17, 2001); In The Matter of Huibert M Vriesendorp, M.D., Commissioner’s Decision (December 31, 2001). See also, Commissioner’s Decision, In the Matter of William H Ziering, M.D. (2008). (<http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm143242.htm>).

³ See, e.g., Commissioner’s Decision, In the Matter of James A. Halikas (2001), at page 23 (“[T]o interpret repeatedly to mean transgressions in more than one study would permit an investigator to commit as many violations of the regulations as he/she wished without possibility of disqualification as long as that investigator limited his/her violations to one study. Such a result * * * would be absurd.”) (<http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm143242.htm>). See also Commissioner’s Decision, In the Matter of Layne O. Gentry (2008), at page 23. (<http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM143906.pdf>).

The term “deliberately” includes conduct that is “willful” as well as conduct demonstrating reckless disregard.⁴ Accordingly, when a clinical investigator knowingly fails to comply with FDA’s regulations, the clinical investigator may be found to have deliberately violated the regulations. FDA could pursue the disqualification of a clinical investigator, for example, if the investigator changed a study’s results by altering a data field on a case report form to include false data. Likewise, an investigator who shows a reckless disregard for whether his or her conduct may result in a regulatory violation may be found to have deliberately violated the regulations.

Decisionmakers in part 16 proceedings have interpreted the term “deliberately” in § 312.70(b) as roughly synonymous with the “deliberate indifference” or “willful” standard of intent.⁵ This standard does not require specific knowledge that behavior, such as submission of false data to a study sponsor, violates the law, but reckless disregard for what the regulations require. The Commissioner’s decision *In the Matter of Layne O. Gentry*⁶ provides a useful discussion of the standard for “deliberate” behavior in a disqualification proceeding:⁷

* * * the term “deliberate,” when used to describe a category of violations that might lead to legal consequences, does not necessarily require a showing of subjective intent on the part of the person in question. * * * the purpose of [disqualification] is to protect the safety of patients and to preserve the integrity of the data needed to assess the

⁴ In *The Matter of James A. Halikas, Jr., M.D.*, Commissioner’s Decision (January 17, 2001); In *The Matter of Huibert M. Vriesendorp, M.D.*, Commissioner’s Decision (December 31, 2001); In *The Matter of Layne O. Gentry, M.D.*, Presiding Officer Report (September 12, 2001). (See <http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm143242.htm>).

⁵ See, e.g., Commissioner’s Decision, In the Matter of William H Ziering, M.D. (2008), at page 8 (“A clinical investigator may be found to have acted ‘deliberately’ * * * if he or she knowingly or willfully engaged in conduct that violates FDA’s regulations or if the investigator engaged in conduct that demonstrated a reckless disregard for compliance with FDA’s regulations.”) See

<http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM144019.pdf>.

⁶ On June 18, 2008, Dr. Gentry was determined ineligible to receive investigational drugs. See <http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM143906.pdf>.

⁷ *Id.* at pages 20-21.

safety and effectiveness of drugs before being sold to the general public through disqualifying investigators who do not fulfill the responsibilities imposed on them.

In the context of such a remedial, as opposed to punitive, scheme, an objective standard for “deliberate” or “deliberately” is a better fit because the inquiry should focus on preventing risk rather than imposing punishment for culpable conduct. Even if the investigator did not intend for the violations to occur, conduct demonstrating a reckless disregard for the regulatory requirements calls into question the investigator’s fitness for conducting clinical trials. * * *

Therefore, to sustain a finding of repeated or deliberate submission of false information, FDA must show that the clinical investigator repeatedly submitted to the sponsor or to FDA false information, whether in a single study or in multiple studies, or submitted false information to the sponsor or FDA knowingly or willfully or with reckless disregard for the truthfulness of the data submitted.

(Comment 2) The comment asks how far back FDA will investigate FDA-approved products with a disqualified investigator’s data; and requests an explanation of how FDA handles products that have been on the market for a longer period of time without significant safety concerns.

(Response) FDA uses its best efforts to identify each application and submission to FDA that may include data from a disqualified clinical investigator. FDA does not place limits on how far back FDA will investigate to find those applications and submissions that may be affected by a disqualified investigator who conducted trials with FDA-regulated test articles.

Each application or submission identified as containing data reported by a disqualified investigator is subject to examination to determine whether the investigator has submitted

unreliable data that are essential to the approval of a marketing application or essential to the continued marketing of an FDA-regulated product. (See §§ 312.70(c), 511.1(c)(3), and 812.119(c)). This examination may be undertaken by FDA or the study sponsor. If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the product for which the data were submitted cannot be justified, the Commissioner will proceed to rescind clearance or withdraw approval of the product in accordance with the applicable provisions of the relevant statutes. (See §§ 812.119(e), 511.1(c)(5), and 312.70(e)).

Often, there may be sufficient data from sources other than the disqualified investigator's data to support the continued approval of the product. Those products that have been on the market for a longer period of time without significant safety concerns, even though a disqualified investigator contributed to the data relied on for approval, would probably remain on the market if sufficient reliable product-approval data support the continued approval of the product.

(Comment 3) The comment asks that FDA promptly inform affected sponsors of an investigator's disqualification.

(Response) FDA agrees that sponsors should be informed promptly about the disqualification of a clinical investigator. Indeed, FDA informs sponsors at several stages of the disqualification process. When FDA initiates a disqualification action, FDA sends to the clinical investigator a notice of initiation of disqualification proceedings and opportunity to explain (NIDPOE) letter. Following confirmed receipt of the NIDPOE letter by the clinical investigator, FDA provides a redacted copy of the letter to the study sponsor and reviewing institutional review boards (IRBs) (see Ref. 2, section II.C., at page 8), and posts the redacted NIDPOE letter

on FDA's Web site.⁸ The posted NIDPOE letter is intended to inform sponsors and others who may have an interest that FDA is initiating an administrative proceeding to determine whether the clinical investigator should be disqualified from receiving test articles.

If the investigator's explanation is not accepted by FDA or if the investigator fails to respond to the NIDPOE letter within the specified time period, FDA offers the investigator an opportunity for an informal regulatory hearing under part 16 to determine whether the investigator should remain eligible to receive test articles. FDA initiates a part 16 hearing by sending to the investigator a Notice of Opportunity for Hearing (NOOH). The NOOH specifies the facts and other relevant information that are the subject of the part 16 hearing (see Ref. 2, id.). FDA posts on its Web site⁹ the names of clinical investigators who have been issued a NOOH concerning a disqualification proceeding along with the redacted NOOH.

If the investigator is disqualified, after receiving confirmation that the investigator has been notified of his or her disqualification, FDA promptly posts on its Web site¹⁰ the investigator's name and the date of the disqualification action. In addition, FDA notifies the study sponsor and reviewing IRBs, in writing, about the disqualification action (Ref. 2, id.). This notification provides a statement of the basis for the Commissioner's disqualification determination (see §§ 312.70(b), 511.1(c)(2), and 812.119(b)).

FDA recommends that sponsors routinely check FDA's compliance and enforcement Web sites¹¹ for information about investigator disqualification proceedings that might affect the sponsor's studies. Further, in compliance with a sponsor's responsibilities (see, e.g., §§ 312.53(a), 511.1(b)(7)(i), and 812.43(a)), a sponsor must select only investigators qualified by

⁸ See <http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm092185.htm>.

⁹ See <http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm143240.htm>.

¹⁰ See <http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/ucm131681.htm>.

¹¹ See <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm>.

training and experience as appropriate experts to investigate the study. A sponsor therefore must perform due diligence to ensure that an investigator is eligible to receive the test article. FDA considers checking FDA's Web site for investigator disqualification to be part of a sponsor's due diligence effort before selecting a clinical investigator to conduct a sponsor's study.

(Comment 4) The comment recommends that FDA consider the impact of investigator disqualification on the submission of results from failed investigations to ClinicalTrials.gov.

(Response) The comment is beyond the scope of this rulemaking as the National Institutes of Health (NIH) has the statutory responsibility for implementing the provisions under the Public Health Service Act, section 402(j), 42 U.S.C. 282(j)--Expanded Clinical Trial Registry Data Bank. The NIH proposes to issue new regulations¹² that will prescribe procedures for registering and reporting the results of clinical trials at ClinicalTrials.gov in accordance with section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA, Public Law 110-85, September 27, 2007).

(Comment 5) The comment recommends that FDA seek input from affected sponsors regarding the impact of a clinical investigator's disqualification on the validity of clinical trial or marketed product data.

(Response) As discussed in response to Comment 2 in this document, upon disqualification of a clinical investigator, each application or submission to FDA containing data reported by a disqualified investigator is subject to examination (see §§ 312.70(c), 511.1(c)(3), and 812.119(c)). We agree that FDA may seek input from an affected study sponsor; for example, FDA may request from the study sponsor statistical analyses of study results after eliminating from the database the disqualified investigator's data.

¹² See the Fall 2011 Unified Agenda, Expanded Registration and Results Reporting at ClinicalTrials.gov (RIN 0925-AA55), at <http://reginfo.gov/public/do/eAgendaViewRule?pubId=201110&RIN=0925-AA55>.

(Comment 6) The comment asks FDA to clarify whether the rule applies to “all sponsors for whom the investigator did work, or only those that were subject to the problem that caused the disqualification.”

(Response) This final rule applies to all sponsors who selected the clinical investigator to conduct their studies. FDA will assess the reliability of any data developed by a disqualified clinical investigator.

(Comment 7) The comment recommends that, because clinical investigator disqualification by a Commissioner’s decision is a lengthy proceeding, FDA consider instituting a process similar to a clinical hold “to prevent these individuals from continuing to conduct clinical trials while the disqualification process is underway.”

(Response) FDA agrees that the use of a clinical hold following clinical investigator misconduct may be appropriate in some situations and has issued a guidance document indicating this (see Ref. 3). For example, FDA may impose a clinical hold on studies where the hold is necessary to protect human subjects in the study from an unreasonable and significant risk of illness or injury. In such a case, FDA may impose a clinical hold based on credible evidence that a clinical investigator conducting the study has committed serious violations of FDA regulations on clinical trials of human drugs and biologics, including parts 312, 50, and 56 (21 CFR parts 50 and 56), or has submitted false information to FDA or the sponsor in any required report. Such a clinical hold may be imposed on the study in which the misconduct occurred or on other studies of drugs or biological products in which the clinical investigator is directly involved or proposed to be involved if FDA determines that the investigator’s misconduct poses an ongoing threat to the safety and welfare of such subjects. (See §§ 312.42(b)(1)(i), 312.42(b)(2)(i), 312.42(b)(3)(iii), and 312.42(b)(4)(i) (Ref. 3).

For medical devices, § 812.30(b) allows for withdrawal of approval of an application for an investigational device exemption (IDE). Under this provision, FDA may withdraw approval of an application if FDA determines that continuation of testing under an IDE will result in an unreasonable risk to subjects.

(Comment 8) The comment recommends that FDA issue guidance on how a disqualified investigator's data in applications and submissions to FDA is to be handled, segregated, analyzed, and reported.

(Response) Because each situation is different, FDA evaluates on a case-by-case basis the best course of action for handling a disqualified clinical investigator's data in applications and submissions. For this reason, FDA does not intend to issue guidance to address how a disqualified investigator's data should be handled.

(Comment 9) The comment recommends that FDA state explicitly in the rule that when an investigator is disqualified by FDA from studies of veterinary drugs the investigator should also be ineligible to participate in studies of veterinary biologics regulated by the U.S. Department of Agriculture (USDA) under Title 9 of the Code of Federal Regulations; and, likewise, that "USDA should codify a companion rule to state that investigators disqualified from participation in studies of goods regulated by FDA will also be disqualified from investigations of veterinary biologics."

(Response) As stated in the preamble to the proposed rule, FDA may refer pertinent matters to another Federal, State, or local government agency for any action determined appropriate by that agency. Although FDA agrees that affected agencies should be aware of judicial proceedings and regulatory actions taken involving clinical investigators, FDA does not have authority to draft a companion rule to be administered by USDA.

(Comment 10) The comment recommends that FDA notify sponsors when a disqualified clinical investigator has been reinstated.

(Response) We agree that FDA should notify interested parties when a clinical investigator is reinstated as eligible to receive FDA-regulated test articles. Because FDA has no way of knowing who, in particular, may be interested in the reinstatement of a certain investigator, FDA lists on its Web site those investigators who have been reinstated.¹³

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Legal Authority

The purpose of disqualifying investigators who violate the regulations is to preserve the integrity of data needed to assess the safety and effectiveness of an FDA-regulated product before the product is made available to the public, and to protect the safety of study subjects during the conduct of a clinical investigation and patient safety after the approval or clearance of a marketing application.

Although the concept of disqualification is not explicitly mentioned in the FD&C Act, FDA has the authority to disqualify clinical investigators who violate FDA's regulations. The Supreme Court in Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 653 (1973) has recognized that FDA has authority that "is implicit in the regulatory scheme, not spelled out in haec verba" in the statute. As stated in Morrow v. Clayton, 326 F.2d 36, 44 (10th Cir. 1963): "[I]t is a fundamental principle of administrative law that the powers of an administrative agency

¹³ See <http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/ucm131681.htm>.

are not limited to those expressly granted by the statutes, but include, also, all of the powers that may fairly be implied therefrom.”

See Mourning v. Family Publications Service, Inc., 411 U.S. 356 (1973), and National Petroleum Refiners Association v. FTC, 482 F.2d 672 (D.C. Cir. 1973). See also Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); National Nutritional Foods Association v. Weinberger, 512 F.2d 688, cert denied, 423 U.S. 827 (1975); United States v. Nova Scotia Food Products Corp., 568 F.2d 240, 246-248 (2d Cir. 1977); American Frozen Food Institute v. Mathews 413 F.Supp. 548 (D.D.C. 1976) aff’d per curiam, 555 F.2d 1059 (D.C. Cir. 1977); National Confectioners Association v. Califano, 569 F.2d 690 (D.C.Cir. 1978); and National Association of Pharmaceutical Manufacturers v. FDA, 637 F.2d 877 (2d Cir. 1981).

“[R]egulatory acts should be given a practical construction, and one which will enable the agency to perform the duties required of it by Congress.” Federal Deposit Ins. Corp. v. Sumner Fin. Corp., 451 F.2d 898, 904 (5th Cir. 1971). Congressional inaction on proposed legislation that would state expressly an agency’s authority to act does not support an inference that the agency lacks implicit authority to act under existing legislation. Red Lion Broadcasting Co. v. FCC, 395 U.S. 367, 381-382 n. 11 (1969). See also Leist v. Simplot, 638 F.2d 283, 318 (2d Cir. 1980), affirmed sub nom. Merrill Lynch, Pierce, Fenner & Smith v. Curran, 456 U.S. 353 (1982). The Supreme Court has often recognized “the construction of a statute by those charged with its administration is entitled to substantial deference.” United States v. Rutherford, 442 U.S. 544 (1979). Board of Governors of FRS v. First Lincolnwood, 439 U.S. 234, 248 (1978) (the Court’s conclusion “is influenced by the principle that courts should defer to an agency’s construction of its own statutory mandate, Red Lion Broadcasting Co. v. FCC, 395 U.S. at 381; Commissioner v. Sternberger’s Estate, 348 U.S. 187, 199 (1955), particularly when that construction accords with

well established congressional goals.” 439 U.S. at 251); Bayside Enterprises, Inc. v. NLRB, 429 U.S. 298, 304 (1977); Udall v. Tallman, 380 U.S. 1, 16 (1965).

Under section 701(a) of the FD&C Act (21 U.S.C. 371(a)), the Commissioner is empowered to issue regulations for the efficient enforcement of the FD&C Act. Regulations issued by the Commissioner under section 701(a) of the FD&C Act for determining whether a clinical investigation of a drug intended for human use, among other things, was scientifically reliable and valid to support approval of a new drug, have been upheld by the Supreme Court (Weinberger v. Hynson, Westcott & Dunning, Inc.); see also Upjohn Co. v. Finch, 422 F.2d 944 (6th Cir. 1970); and Pharmaceutical Manufacturers Association v. Richardson, 318 F.Supp. 301 (D.Del. 1970)).

Furthermore, sections 505(i), 512(j) and 520(g) of the FD&C Act (21 U.S.C. 355(i), 360b(j), and 360j(g)) regarding clinical investigations that require prior FDA authorization direct the Commissioner to issue regulations to protect the public health in the course of those investigations. Also, sections 505(i)(1), 512(j), and 520(g)(2)(A) of the FD&C Act require that investigations be conducted by “experts qualified by scientific training and experience.” An investigator who repeatedly or deliberately violates the regulations or who repeatedly or deliberately submits false information would not be considered a qualified expert with the experience required to conduct investigations of FDA-regulated articles. Among other stated objectives, the final rulemaking is intended to fulfill those mandates.

The Commissioner therefore concludes that legal authority to issue those regulations regarding clinical investigators exists under sections 505(i), 512(j), 520(g) and 701(a) of the FD&C Act, as essential to protection of the public health and safety and to enforcement of the Agency’s responsibilities under sections 409, 502, 503, 505, 506, 510, 512, 513, 514, 515, 518,

519, 520 and 801 of the FD&C Act (21 U.S.C. 348, 352, 353, 355, 356, 360, 360b, 360c, 360d, 360e, 360h, 360i, 360j and 381), as well as the responsibilities of FDA under section 351 of the Public Health Service Act (42 U.S.C. 262).

VI. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). In accordance with Executive Order 12866, FDA has previously analyzed the potential economic effects of this final rule. As announced in the proposal, the Agency has determined that the rule is not a significant regulatory action as defined by Executive Order 12866. The Agency has not received any new information or comments that would alter its previous determination.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule does not impose new requirements on any entity and therefore has no associated compliance costs, the Agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure

by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

Synopsis

This rule expands the scope of FDA’s disqualification actions so that a disqualified clinical investigator is ineligible to receive any FDA-regulated test article and ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA. We estimate that there is an average of about one matter per year in which clinical investigators are ultimately disqualified via a Commissioner’s decision, and we do not expect that this final rule will impose additional costs. Non-quantifiable benefits of this final rule would include helping to reduce the risk of additional violations in other FDA-regulated investigations and helping to ensure the integrity of clinical trial data. This final rule will help to reduce the risk to human subjects who participate in FDA-regulated investigations, and may lead to improved public confidence in the clinical data supporting FDA decisions. The full analysis of impacts is presented in Ref. 4 of this document.

VII. Paperwork Reduction Act of 1995

This final rule contains no new collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

The information collection in § 312.70 pertaining to the disqualification of a clinical investigator and an investigator’s opportunity to respond to FDA is approved under the investigational new drug regulations, OMB Control No. 0910-0014; expiration date February 28,

2013.¹⁴ The notification of IRBs in § 312.70 is approved under OMB Control No. 0910-0130--Protection of Human Subjects; Recordkeeping Requirements for Institutional Review Boards (IRBs); expiration date April 30, 2014.¹⁵ The information collection in § 511.1(c) pertaining to the disqualification of a clinical investigator and an investigator's opportunity to respond to FDA is approved under the new animal drugs for investigational use regulations OMB Control No. 0910-0117; expiration date August 31, 2011 (renewal pending at OMB).¹⁶ The information collection in § 812.119 pertaining to the disqualification of a clinical investigator and an investigator's opportunity to respond to FDA is approved under the investigational device exemptions reports and records in 21 CFR part 812, OMB Control No. 0910-0078; expiration date February 28, 2013.¹⁷ In addition, INDs and new drug applications are approved under OMB control number 0910-0416; animal drug applications, 21 CFR part 514, are approved under OMB control number 0910-0032; premarket notification submissions 510(k), subpart E, are approved under OMB control number 0910-0120; and premarket approvals of medical devices, 21 CFR part 814, are approved under OMB control number 0910-0231.

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the rule does not contain policies that have

¹⁴ See http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200905-0910-005 (accessed on March 30, 2012).

¹⁵ See http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200711-0910-003 (accessed on March 30, 2012).

¹⁶ See http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200806-0910-005 (accessed on March 30, 2012).

¹⁷ See http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=201001-0910-010 (accessed on March 30, 2012).

federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. References

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. GAO Report to Congressional Requesters--Oversight of Clinical Investigators, Action Needed to Improve Timeliness and Enhance Scope of FDA's Debarment and Disqualification Processes for Medical Product Investigators; GAO-09-807. See <http://www.gao.gov/new.items/d09807.pdf>.
2. See "Information Sheet Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Clinical Investigator Administrative Actions--Disqualification," May 2010, at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214008.pdf>.
3. See "Guidance for Industry and Clinical Investigators: The Use of Clinical Holds Following Clinical Investigator Misconduct," September 2004, at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126997.pdf>.
4. Full Analysis of Impacts of Final Rule.

List of Subjects

21 CFR Part 16

Administrative practice and procedure.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 511

Animal drugs, Medical research, Reporting and recordkeeping requirements.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 16, 312, 511, and 812 are amended as follows:

PART 16--REGULATORY HEARING BEFORE THE FOOD AND DRUG
ADMINISTRATION

1. The authority citation for 21 CFR part 16 continues to read as follows:

Authority: 15 U.S.C. 1451-1461; 21 U.S.C. 141-149, 321-394, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201-262, 263b, 364.

2. Section 16.1 is amended in paragraph (b)(2) by numerically adding entries for “§ 58.204(b)”, “§ 812.119”, and “§ 822.7(a)(3)”, and by revising the entries for “§ 312.70” and “§ 511.1(c)(1)” to read as follows:

§ 16.1 Scope.

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(b) * * *

(2) * * *

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§ 58.204(b), relating to disqualifying a testing facility.

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§ 312.70, relating to whether an investigator is eligible to receive test articles under part 312 of this chapter and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

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§ 511.1(c)(1), relating to whether an investigator is eligible to receive test articles under part 511 of this chapter and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

* * * * *

§ 812.119, relating to whether an investigator is eligible to receive test articles under part 812 of this chapter and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

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§ 822.7(a)(3), relating to an order to conduct postmarket surveillance of a medical device under section 522 of the act.

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PART 312--INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

4. Section 312.70 is revised to read as follows:

§ 312.70 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50 or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the Center will discontinue the disqualification proceeding. If an explanation is offered but not accepted by the applicable Center, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is eligible to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50 or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required

report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing institutional review boards (IRBs) that the investigator is not eligible to receive test articles under this part. The notification to the investigator, sponsor, and IRBs will provide a statement of the basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(c) Each application or submission to FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of an investigation or essential to the approval of a marketing application, or essential to the continued marketing of an FDA-regulated product.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor, who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor and the reviewing IRBs of the termination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the

question of whether the IND should be reinstated. The determination that an investigation may not be considered in support of a research or marketing application or a notification or petition submission does not, however, relieve the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the product in accordance with the applicable provisions of the relevant statutes.

(f) An investigator who has been determined to be ineligible under paragraph (b) of this section may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

PART 511--NEW ANIMAL DRUGS FOR INVESTIGATIONAL USE

5. The authority citation for 21 CFR part 511 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 360b, 371.

6. Section 511.1 is amended by:

a. Removing “the Food and Drug Administration” and adding in its place “FDA” in paragraph (b)(4) introductory text, and paragraphs (b)(5)(iii), (b)(6), (b)(8)(ii), (b)(9)(i), (d)(2), and (f)(1).

b. Revising paragraph (c).

The revisions read as follows:

§ 511.1 New animal drugs for investigational use exempt from section 512(a) of the act.

* * * * *

(c) Disqualification of a clinical investigator. (1) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the conditions of these exempting regulations or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Center for Veterinary Medicine will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the Center for Veterinary Medicine, the Center will discontinue the disqualification proceeding. If an explanation is offered but not accepted by the Center for Veterinary Medicine, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is eligible to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

(2) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations in this subchapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not eligible to receive test articles under this part. The notification to the investigator and sponsor will provide a statement of the basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to

conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(3) Each application or submission to FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of an investigation or essential to the approval of a marketing application, or essential to the continued marketing of an FDA-regulated product.

(4) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor, who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the exemption immediately and notify the sponsor of the termination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the exemption should be reinstated. The determination that an investigation may not be considered in support of a research or marketing application or a notification or petition submission does not, however, relieve the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(5) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the product for

which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the product in accordance with the applicable provisions of the relevant statutes.

(6) An investigator who has been determined to be ineligible under paragraph (c)(2) of this section may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

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7. Section 511.3 is added to read as follows:

§ 511.3 Definitions.

As used in this part:

Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. “Subinvestigator” includes any other individual member of that team.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct

the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

PART 812--INVESTIGATIONAL DEVICE EXEMPTIONS

8. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b-263n.

9. Section 812.119 is revised to read as follows:

§ 812.119 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, or the Center for Drug Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the Center will discontinue the disqualification proceeding. If an explanation is offered but not

accepted by the applicable Center, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is eligible to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing investigational review boards (IRBs) that the investigator is not eligible to receive test articles under this part. The notification to the investigator, sponsor and IRBs will provide a statement of the basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(c) Each application or submission to FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of an investigation or essential to

the clearance or approval of a marketing application, or essential to the continued marketing of an FDA-regulated product.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor, who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the investigational device exemption (IDE) immediately and notify the sponsor and the reviewing IRBs of the termination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 of this chapter on the question of whether the IDE should be reinstated. The determination that an investigation may not be considered in support of a research or marketing application or a notification or petition submission does not, however, relieve the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued clearance or approval of the product for which the data were submitted cannot be justified, the Commissioner will proceed to rescind clearance or withdraw approval of the product in accordance with the applicable provisions of the relevant statutes.

(f) An investigator who has been determined to be ineligible under paragraph (b) of this section may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct

any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

Dated: April 24, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

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